REMARKS

Amendments to the Claims

With this response, claims 1, 13-15, 22, 28, 43-46, 50-53 and 57-60 are amended, claim 11 is cancelled and claim 61 is added. Claims 1, 28, 45 and 46 have been amended to specify that the method utilizes two or more intravenous administrations of the subject antibody. These amendments are supported by the specification, *inter alia*, at page 41, line 25 to page 42, line 22; and page 46, line 25 to page 47, line 25. Claims 13-15, 22, 50-53 and 57-60 are amended to correct formal matters. New claim 61 corresponds to previously canceled claim 29.

Claims 1, 6-10, 12-16, 22, 28 and 32-61 will be pending and under consideration after entry of the present amendment. No new matter is added.

Withdrawn Rejections

The Applicants respectfully note the withdrawal of the following rejection:

- the rejection of claims 10, 32 and 41 under 35 U.S.C. § 112, first paragraph, regarding the biological deposit requirement;

Inventorship Change

The addition of claim 61 (reinstated claim 29) necessitates changing the inventorship of the present application to also name Dr. Mark Pescovitz. The Applicants previously noted that Dr. Pescovitz is the sole inventor of the subject matter of cancelled claim 29. In order to update inventorship, the following documents accompany this submission: (1) Request to Correct Inventorship under 37 C.F.R. § 1.48(a); (2) Statement under 37 C.F.R. § 1.48(a)(2) by Mark D.

Peskovitz; (3) Declaration under 37 C.F.R. § 1.63 and Power of Attorney; (4) written consent of the assignees Genentech, Inc. and Biogen Idec, Inc. under 37 C.F.R. § 1.48(a)(5) to add an inventor; and (5) the processing fee set forth under 37 C.F.R. § 1.17(i).

Objection to the Claims

The Examiner has stated that "should claims 43, 50 and 52-53 be found allowable, claims 51 and 57-60 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof." Claims 51 and 57-60 are amended herein to update their dependency. Accordingly this objection is rendered moot.

Rejection Under 35 U.S.C.§ 102(b)

Claims 1, 6, 11-16, 22, 28, 34-39, 43-48, 50-55 and 57-60 stand under 35 U.S.C. §102(b) as purportedly anticipated by WO 98/04281 (hereafter "Davis").

The Applicants respectfully maintain the position set out in the previous reply with regard to this rejection, regardless of the present claim amendments. However, since the present claims are now additionally distinguishable from these claims in that they require blocking an immune response to an allogeneic graft or a method of treating graft-versus-host or host-versus-graft disease in a human via a plurality of intravenous administrations of an antibody that binds to the CD20 antigen on human B lymphocytes, another basis distinguishing the claims from the cited art is provided. Specifically, Davis et al. does not describe a method in which an anti-CD20 antibody is intravenously administered more than one time to a patient to block an immune response to an allogeneic graft or treat graft-versus-host or host-versus-graft disease, wherein each administration is of a therapeutically effective dose which results in depletion of

circulating B-cells in the patient. Instead, the essential teaching of Davis et al. is of a method in which a first *non-therapeutic* dose is administered to enable subsequent *subcutaneous* administration of a therapeutic amount of the antibody.

The Examiner asserts that claims 19, 23 and 31 in the published PCT application discloses the presently claimed methods which require the multiple, intravenous administration of anti-CD20 antibodies to block an immune response to an allogeneic graft or to treat graft-versus-host or host-versus-graft disease in a human. As explained in the previous office action, claims 19 and 23 –even if they were to be found to enable what they ostensibly set forth, which they do not – do not suggest or describe methods in which an anti-CD20 antibody is administered to block an immune response to an allogeneic graft or to treat graft versus host disease in a human. As explained in the previous office action, the published claims from which these two claims depend ultimately derive from claim 1 in the published PCT application, which reads:

> 1. An improved method for treating immune cell mediated diseases wherein. the improvement comprises: [i] administering a saturating dose of a therapeutic protein selected from the group consisting of a monoclonal antibody, a soluble receptor and a soluble ligand which binds to an antigen expressed on the surface of an immune cell; followed by a second administration of said therapeutic protein, [ii] wherein the second administration is given subcutaneously, and [iii] wherein the systemic exposure of said therapeutic protein from the second administration is at least 50% greater than the systemic exposure from a first, and equivalent, subcutaneous dose of the therapeutic protein. [emphasis and numbering added]

The published dependent claims (19 and 23) thus (i) require that a "saturating dose" be administered first, (ii) that the second administration of the agent be by subcutaneous means only, and (iii) a particular result of the second administration result (i.e., that the systemic exposure of the therapeutic protein in the second administration be at least 50% greater than the systemic exposure of the first administration of the therapeutic protein. To the extent that the

Examiner believes it appropriate to cite the claims of this published PCT application for any purpose, he must at least adhere to what the actual text of the cited claims recites. Because the recited claims do not describe a process that meets all of the requirements of the present claims, the referenced published claims do not anticipate the present claims.

The Examiner also cites claim 31 of the published PCT application for the proposition that it specifically describes a method of treating graft-vs-host disease. Initially, as this claim does not refer to blocking of an immune response to an allogeneic graft, it cannot be characterized in any manner as literally describing a method as defined by claims 1, 6, 11-16, 22, 45, and 47-53). As such, it cannot be portrayed in any way as anticipating any of these claims.

More importantly, neither the claims nor the disclosure of Davis can be described as anticipating any of the present claims because Davis does not describe, in a manner sufficient to anticipate, the presently claimed methods. Simply put, Davis et al. cannot anticipate the present claims because, as indicated above, it is not enabled for the specific purpose it is relied upon by the Examiner. As acknowledged by the Federal Circuit, "[a] claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003) (citing *In re Borst*, 145 USPQ 554, 557 (C.C.P.A. 1962)).

As noted previously, the examples provided in Davis et al. concern an antibody that binds to the CD4 antigen, which is found on T lymphocytes. In particular, Davis et al. exemplifies treatment only of mice with a CD4 monoclonal antibody. In this respect, Applicants note that U.S. Application No. 09/905,836 (the '836 application), a National Stage § 371 application of PCT/US97/12600 (WO 98/04281), is equivalent to WO 98/04281 (*see* enclosed Exhibit A –

Declaration and Power of Attorney filed in connection with U.S. Application No. 09/905,836). During prosecution, the '836 applicants canceled all claims of the PCT application and directed them to a method of treating T-cell lymphocyte mediated diseases using an anti-CD4 antibody by administering a first (saturating) and second (therapeutic) dose of this antibody (*see* Exhibit A – '836 application preliminary amendment). The '836 applicants thereafter elected and pursued claims to treatment of the "rheumatoid arthritis" species of T-cell lymphocyte mediated disease (*see* Exhibit A – '836 application restriction and restriction reply).

The Examiner of the '836 application, Phillip Gambel and Supervisory Examiner Christina Chan (Art Unit 1644), thereafter rejected the claims (i.e., directed to administration of anti-CD4 antibodies to treat rheumatoid arthritis) *as being neither described nor enabled* (*see* Exhibit A – '836 application Office action). In particular, the Examiner indicated that the '836 application *does not adequately describe nor enable treating humans with CD4 antibodies nor "a saturating dose" as defined in the specification for in vivo use due to the inadequate disclosure and lack of predictability in the art*. The application was subsequently abandoned without reply by the '836 applicants (see Exhibit A – '836 application Notice of Abandonment).

The Office's findings are important in the present situation because it is clear that the *only* examples in the entire Davis et al. disclosure actually discussed in any detail are those directed to treatments using anti-T lymphocyte specific antibodies, *not anti-B cell, nor anti-CD20 antibodies* – and claims to the use of these T-cell antibodies were found by the Office *to not be enabled*. Clearly, therapeutic uses of anti-B cell or anti-CD20 antibodies, since there are *no* working examples directed to these, cannot be enabled either.

Based on the foregoing it is also apparent that Davis et al. similarly fails to present an inherent disclosure of the present claims. As provided by the Federal Circuit, inherent anticipation requires that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citing *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) ("The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Id.* (emphasis in original)). Thus, inherency *does not embrace probabilities or possibilities. See id.*

As previously indicated and as indicated above, there is no disclosure (explicit or inherent) in Davis et al. of administration an antibody that binds to the CD20-antigen to block an immune response to an allogeneic graft and/or to treat graft-versus-host disease. The Examiner's apparent belief that that administration of any type of antibody that binds to any immune cell, or more particularly, to any B-cell surface antigen, will inherently provide the same results as presently claimed methods is not supported by any known scientific or other rationale. For example, it is known that numerous antigenic targets can be found on B-lymphocytes. Certain of these antigenic targets are present on only certain subpopulations of B-lymphocytes (e.g., depending on whether the B-lymphocyte is naïve or mature). Certain antigenic determinants found on B-lymphocytes are also found on other types of cells. Administration of one antibody that binds to one antigenic determinant on B-lymphocytes will not necessarily bind to the same population of B-lymphocytes as those bound by first antibody. The physiological consequences of these different binding patterns plainly will not be identical. Thus, unless the Examiner can cite evidence to suggest that identical therapeutic responses result from administration of any

type of antibody that binds to an antigen on a B-lymphocyte, it is legally improper to suggest that the Davis publication inherently anticipates the presently claimed methods.

The Examiner also appears to assert that the use of the claim term "comprising" opens the claims to encompass presumably all types of administration contemplated in the present disclosure. In this regard, the Applicants respectfully point out that it is improper to utilize "comprising" language to effectively eliminate specifically recited claim limitations. "The term 'comprising' denotes a patent claim as being 'open,' meaning that the recitation of structure in the claim is open to additional . . . elements not explicitly mentioned." *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1271, 229 USPQ 805, 812 (Fed. Cir. 1986) (emphasis added). However, "*[c]omprising" is not a weasel word with which to abrogate claim limitations.*" *Id.* (emphasis added). *See also Spectrum International Inc. v. Sterilite Corp.*, 49 USPQ2d 1065, 164 F3d 1372 (Fed. Cir. 1998).

In re Crish, 73 USPQ2d 1364 (Fed. Cir. 2004), cited by the Examiner, actually supports Applicants', not the Examiner's, point. In *Crish* the claims were found to require "at least a portion of SEQ ID NO:1," which portion was specifically recited in the "wherein" clause of the claims at issue, "but the . . . term "comprising" means that the claim can include *that portion plus other nucleotides*." *Crish* at 1367 (emphasis added). Importantly, the *Crish* Court found that the claims required *at least* the specifically recited nucleotide portion and *did not* find that this specific portion is *optional*. In that case, the distinction was important because the prior art disclosed the recited portion plus additional portions. In contrast, in the present case, the present claims specify that each administration of the antibody is by intravenous administration – however, as acknowledged by the Examiner (*see* page 3 of the July 28, 2004 Office action), Davis et al. fails to teach intravenous administration.

Finally, to the extent that the Examiner has based the present rejection on the view that the administration of a saturating dose versus a therapeutic dose is immaterial, the Examiner is respectfully invited to more carefully review the Davis et al publication. For example, Davis explains that

> A saturating dose" refers to the amount of therapeutic protein necessary to completely bind a selected immune cell antigen in the lymphatic system such that no appreciable binding of the therapeutic protein to the immune cell antigen occurs upon subsequent administration(s) of the therapeutic protein. *The amount of therapeutic protein needed will vary according to the amount of immune cell antigen present in the lymphatic system, the affinity of the therapeutic protein for such antigen, and the half-life of the therapeutic protein in vivo*. One skilled in the art will be able to identify the appropriate amount of the therapeutic protein. For example, for a human anti-CD4 monoclonal antibody, the saturating dose will typically be in the range of 0.5 to 5 mg/kg. (emphasis added)

According to the explicit guidance of Davis, the amount of a "saturating" dose of any type of immune-cell specific antibody will not be identical, or any amount within the range of 0.5 to 5 mg/kg. Rather, the amount of the "saturating dose" for one type of antibody will differ than the "saturating" dose of another antibody. Davis instructs the person of skill in the art to determine the amount of an antibody that should be administered to meet the requirement that it be a saturating dose. Thus, Davis does not teach a person of skill to administer the full range of possible amounts of an antibody to a patient, regardless of the antigen to which the antibody binds, the role of the immune cell in the disease or disorder, or any of a number of other parameters. Thus, Davis does not teach administration of anti-B cell antibodies, for example, in the full range of possible amounts for any type of antibody, as the Examiner suggests.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C.§ 102(b) over Davis et al.

35 U.S.C. §103 Rejection over Davis in view of Business Wire

The Examiner has rejected claims 1, 7-10, 28, 32, 40, 41, 45-46, 49 and 56 under 35 U.S.C. §103(a) as unpatentable over Davis et al. in view of Business Wire (2/24/1998).

Applicants respectfully submit that the Davis et al. and Business Wire references, taken alone or together, would not have rendered the presently claimed methods obvious to a person of skill in the art. As indicated above, there is no suggestion, let alone a specific disclosure, in Davis et al. of administration of a plurality of intravenous doses of an antibody, which binds to the CD20-antigen and reduces the circulating levels of B cells, to treat graft rejection and/or graft-versus-host disease.

The deficiencies of Davis et al. relative to the present claims are not remedied by the teaching of the Business Wire article. Instead, the Business Wire article merely reports on initiation of a Phase III trial incorporating both of IDEC Pharmaceutical's treatments for relapsed or refractory B-cell non-Hodgkin's lymphoma, IDEC-Y2B8, and the approved immunotherapy, RITUXAN®. RITUXAN® is disclosed as being used in the regimen to clear malignant and normal B cells from the blood, allowing IDEC-Y2B8 to penetrate the lymphatic system and target radiation to lymphatic tumors.

There is no discussion in the Business Wire article of use of antibodies to the CD20 antigen to treat graft rejections or graft-versus-host disease. One of ordinary skill thus would not look to Business Wire for guidance in altering the methods and disclosure of Davis et al., either to select an antibody to CD20 to block immune responses to allogeneic grafts or to treat graft-versus-host disease, or to devise a new treatment regimen where upon each administration of the antibody, circulating levels of B cells would be reduced in the patient to exhibit the desired

therapeutic effect. Applicants also maintain that even armed with knowledge that rituximab achieves selective depletion of B-lymphocytes in patients with B-cell lymphomas, such as non-Hodgkin's lymphoma, a person of skill would not have been motivated from the Business Wire article or Davis et al. to arrive at the presently claimed methods.

As indicated above, Davis et al. does not even enable treatment of rheumatoid arthritis using an anti-CD4 antibody, let alone treatment of graft rejections or graft-versus-host disease using an anti-B cell or anti-CD20 antibody. The Business Wire article is unavailing. Assuming *arguendo* that one were motivated to look to the Business Wire article, there is no indication of which selection of the numerous methods, reagent and dose parameters must be varied and utilized to treat graft rejections or graft-versus-host disease. In view of the lack of predictability of the art to which Davis et al. was directed and the lack of established clinical protocols for effective antibody-based therapies based upon saturating doses, one of skill would not have had a reasonable expectation of success of treating treat graft rejections or graft-versus-host disease by administering an antibody that binds to the CD20 antigen on human B lymphocytes based on the Davis et al. and Business Wire disclosures.

For the reasons set forth above, Davis et al. does not teach or suggest the limitations of the present claims. The teachings of the Business Wire article do not cure the fundamental defects of Davis et al. Accordingly, Applicants accordingly requests withdrawal of this rejection.

35 U.S.C. §103 Rejection over Davis in view of US Patent No. 6,498,181

The Examiner has maintained the rejection of claims 1, 8-10, 28, 33, and 42 under 35 U.S.C. §103(a) as unpatentable over WO 98/04281 ("Davis et al.") in view of U.S. Patent No. 6,498,181 (hereafter "Gehlsen").

Applicants respectfully submit that the Davis et al. and Gehlsen references, taken alone or together, would not have rendered the presently claimed methods obvious to a person of skill in the art. As indicated above, there is no suggestion, let alone a specific disclosure, in the Davis et al. disclosure of administration of a plurality of intravenous doses of an antibody, which binds to the CD20-antigen and reduces the circulating levels of B cells, to treat graft rejection and/or graft-versus-host disease.

Gehlsen does not cure the deficiencies of Davis et al. Instead, Gehlsen is directed to methods of treating cancer. The cancer therapy includes surgery, radiation, immunotherapy, and the administration of an agent which enhances the humoral response of the patient or any combination thereof. At col. 9, lines 3-12, Gehlsen teaches that histamine can be administered in conjunction with an antibody therapy. Gehlsen teaches:

> According to the one aspect of this embodiment, a radioactive monoclonal antibody is administered in conjunction with histamine. Preferably, histamine is administered for 1-2 weeks before the antibody therapy to raise the stable concentration of histamine in the patient's blood to at least about 0.2μM. After a stable level of blood histamine of at least about 0.2μM has been achieved, a radiolabeled mAb directed to a cancer cell antigen is administered in conjunction with histamine treatment to the patient.

At col. 9, lines 22-28, Gehlsen teaches:

> Preferable radiolabeled mAbs are able to deliver more than 6000 rads to the tumor and have sufficient affinity so that the patient's bone marrow is not exposed to more than 300 rads. ^{131}I labeled anti-B1(Bexxar) mAb, raised to the CD-20

> antigens that are expressed on the surface of mature B-cells, is one example of a radiolabeled mAb that has seen successful in treating follicular non-Hodgkins lymphoma in recent clinical trials.

One of ordinary skill in the art would not look to Gehlsen for guidance in blocking an immune response to an allogeneic graft or treating graft-versus-host or host-versus-graft disease, in part, because Gehlsen is directed to the use of the Bexxar anti-B1 monoclonal antibody in the treatment of *cancerous* conditions, specifically non-Hodgkins lymphoma. The present claims specifically exclude therapy of malignant or cancerous conditions. (*See, e.g.*, Applicants' specification at page 5, lines 5-6).

As indicated above, Davis et al. does not even enable treatment of rheumatoid arthritis using an anti-CD4 antibody, let alone treatment of graft rejections or graft-versus-host disease using an anti-B cell or anti-CD20 antibody. Gehlsen is unavailing. Assuming *arguendo* that one were motivated to look to Gehlsen, there is no indication of which selection of the numerous methods, reagent and dose parameters must be varied and utilized to treat graft rejections or graft-versus-host disease. In view of the lack of predictability of the art to which Davis et al. was directed and the lack of established clinical protocols for effective antibody-based therapies based upon saturating doses, one of skill would not have had a reasonable expectation of success of treating treat graft rejections or graft-versus-host disease by administering an antibody that binds to the CD20 antigen on human B lymphocytes based on the Davis et al. and Gehlsen disclosures.

Accordingly, the cited publications do not establish a *prima facie* case of obviousness of the rejected claims. Applicants accordingly request withdrawal of this rejection.

Rejections Under 35 U.S.C.§112, Second Paragraph

Claims 1, 6-16, 22, 28, 32-44, 50-51 and 57-58 stand rejected under 35 U.S.C.§ 112, second paragraph as purportedly indefinite. Claims 6-12, 14-16, 32-44, 51 and 58 apparently stand rejected under the recited basis only because they depend from rejected claims. No separate basis for rejection is set forth for any of these additional claims.

The Examiner has stated that the claim phrase "'a first administration' [recited in claims 1 and 28] is ambiguous because a first administration indicates that there are additional administrations", and further that "[i]t is not clear whether . . . there are additional administrations . . ." April 21, 2005 Office Action, p. 9. The Applicants respectfully note that this phrase is descriptive of the consequences of a particular administration of the described antibody and is clear in this regard. Nevertheless, the current claims specify that more than one intravenous dose is administered. Accordingly, this rejection may be withdrawn.

The Examiner has also rejected claims 13, 22, 50 and 57 for the recitation of the term "mammal" as purportedly lacking antecedent basis. Since the "human" term recited in base claims 1 and 45 inherently comprises a "mammal," the Applicants interpret this rejection as merely a formalistic objection. The Applicants thank the Office for pointing out this difference in claim language. Claims 13, 22, 50 and 57 are amended herein to conform the claim language with earlier amendments. Accordingly, this rejection should be withdrawn. It is believed that since the present claim amendments are provided for reasons related to form not necessary for further consideration of the claimed subject matter, they do not affect the resulting claim scope.

Rejections Under 35 U.S.C.§112, First Paragraph

Claims 1, 6-16, 22, 28 and 32-60 stand rejected under 35 U.S.C.§ 112, first paragraph as purportedly not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner states that the phrase "wherein after a first administration" in claim 1 and 28 and the phrase "wherein each administration of the antibody" in claims 45-46 "represent a departure from the specification and claims as originally filed." April 21, 2005 Office Action, p. 9.

Respectfully, the language objected to in claims 1 and 28 is clearly set forth in the specification and claims as filed. For example, page 8, line 24 to page 9, line 4 describe the action of an antagonist of the present invention, which includes the antibodies of the present claims. This section teaches, inter alia, that the antagonist binds the CD20 antigen and, in a preferred embodiment, reduces the level of circulating B cells "in a mammal treated therewith." Thus, a "first administration" is clearly described. Contrary to the Examiner's implication, this descriptive support does not limit the term "treated" to only results achieved in administrations subsequent to the first administration. Nevertheless, the present claim amendments render this rejection moot. Accordingly, this rejection may be properly withdrawn.

With regard to the support for claims 45-46, one of skill in the art would understand page 42, lines 16-22, for example, as clearly describing alternative embodiments of the invention. The Examiner acknowledges that administration via intravenous injection represents a preferred embodiment. April 21, 2005 Office Action, p. 9. Claims 45-46 are directed to particular, preferred embodiments of the invention and thus are adequately described. As the Office is

aware, "[i]n order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue." Purdue Pharma L.P. v. Faulding Inc., 56 USPQ2d 1481, 1483 (Fed. Cir. 2000). Accordingly, this rejection may be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully submit that all pending claims as currently presented are in condition for allowance. If, for any reason, the Examiner disagrees, he is requested to contact the undersigned attorney at 202-736-8914 in an effort to resolve any matter still outstanding *before* issuing another action. Favorable reconsideration is respectfully requested.

In the unlikely event that the Patent Office determines that extensions and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or fees due to our Deposit Account No. **18-1260**, referencing Docket No. **22338-00602**. Any refund should be credited to the same account. The Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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Exhibit A

DECLARA)N AND POWER OF ATTORNEY

As below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

" Improved Method of Treating Immune Cell Mediated Systemic Diseases "

the specification of which (check one)
[] is attached hereto.
[X] was filed on **25 July 1997** as Serial No. **PCT/US97/12600**
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date
60/022,472	26 July 1996

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

Customer Number 20462.

Address all correspondence and telephone calls to Edward R Gimmi, SmithKline Beecham Corporation, Corporate Intellectual Property-U.S., UW2220, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939, whose telephone number is 610-270-4478.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Attorney Docket No. P50497C1

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Bugelski *et al.*

Serial No.: Group Art Unit No.:

Filed: herewith Examiner:

For: IMPROVED METHOD OF TREATING IMMUNE CELL MEDIATED SYSTEMIC DISEASES

PRELIMINARY AMENDMENT

Prior to calculating the filing fee and substantive examination, please amend the above-identified application as follows:

In the claims:

Please cancel claims 1-33, without prejudice, subject to their inclusion in one or more continuing applications.

Please add new claims 34-48 as follows:

--34. An improved method for treating T-cell lymphocyte mediated diseases wherein the improvement comprises: administering a saturating dose of a monoclonal antibody which binds to human CD4 antigen; followed by a second administation of the monoclonal antibody, wherein the second administration is given subcutaneously, and wherein the systemic exposure of the therapeutic protein from the second administration is at least 50% greater than the systemic exposure from a first, and equivalent, subcutaneous dose of the monoclonal antibody.

35. The method of claim 34 wherein the monoclonal antibody is a primate-human chimeric antibody.

36. The method of claim 35 wherein the chimeric antibody is CE9.1

37. The method of claim 34 wherein the monoclonal antibody is a humanized monoclonal antibody.

38. The method of claim 34 wherein the monoclonal antibody is a human monoclonal antibody.

39. The method of claim 34 wherein the disease is rheumatoid arthritis.

40. The method of claim 34 wherein the disease is psoriasis.

41. The method of claim 34 wherein the disease is asthma.

42. The method of claim 34 wherein the disease is graft versus host disease.

43. The method of claim 34 wherein the saturating dose is given intravenously.

44. The method of claim 34 wherein the saturating dose is given intramuscularly.

45. The method of claim 34 wherein the second administration of the monoclonal antibody is given subcutaneously in the upper arm, the surpaclavicular or suprascapular region.

46. The method of claim 34 wherein the second administration of the monoclonal antibody is given subcutaneously in the abdominal wall or upper thigh.

47. The method of claim 34 wherein the systemic exposure of the monoclonal antibody from the second administration is at least 2-fold (i.e., 100%) greater than the systemic exposure from a first, and equivalent, subcutaneous dose of the monoclonal antibody.

48. The method of claim 34 wherein the systemic exposure of the monoclonal antibody from the second administration is at least 4-fold greater than the systemic exposure from a first, and equivalent, subcutaneous dose of the monoclonal antibody.--

REMARKS

Claims 34-48 are pending in the application. It is respectfully requested that examination of the application on the merits proceed.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

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Registration No. 33,833

GLAXOSMITHKLINE
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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

In the Claims:

Claims 1-33 have been cancelled.

New claims 34-48 have been added.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,836	07/13/2001	Peter John Bugelski	P50497C1	3846

7590 08/25/2003

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EXAMINER
GAMBEL, PHILLIP

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action S ıary	09/905836	BUGAISKI
	Examiner GAMBEL	Art Unit 1644

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 7/13/01

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) ____ is/are pending in the application. 34-48

4a) Of the above claim(s) ____ is/are withdrawn from consideration.

5)☐ Claim(s) ____ is/are allowed.

6)☐ Claim(s) ____ is/are rejected.

7)☐ Claim(s) ____ is/are objected to.

8)☑ Claim(s) ____ are subject to restriction and/or election requirement. 34-48

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on 7/13/01 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on ____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. ____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
4)☐ Interview Summary (PTO-413) Paper No(s). ____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

PAPER NO. 4

DETAILED ACTION

1. Applicant's amendment, filed 7/13/01 (Paper No. 3), has been entered.
Claims 1-33 have been canceled.
Claims 34-48 have been added.

2. This application contains claims directed to the following patentably distinct species of the claimed Invention: wherein the T cell lymphocyte-mediated disease is:
A) rheumatoid arthritis,
B) psoriasis,
C) GVHD, or
D) one of the additional T cell lymphocyte-mediated diseases selected from the group disclosed on pages 9-10 of the instant specification (Disease States).

It is noted that pages 9-10 of the instant specification (Disease States) discloses additional T cell lymphocyte-mediated diseases, which are subject to species election.

These species are distinct because the pathological conditions differ in etiologies and therapeutic endpoints.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 34 is generic, for example.

3. Applicant is advised that a response to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. M.P.E.P. § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

4. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703)872-9306.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
August 25, 2003

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below to Facsimile Telephone Number (703)872-9306

Deborah L. Pishock
Type Name of Person Signing Certificate

Deborah L Pishock 9/18/03
Signature Date

Attorney Docket No.: P50497C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Peter John Bugelski	18 September 2003
Serial No.:	09/905,836	Group Art Unit: 1644
Filed:	13 July 2001	Examiner: Phillip Gambel
For:	Improved Method of Treating Immune Cell Mediated Systemic Diseases	

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE OF RESTRICTION REQUIREMENT UNDER 37 C.F.R. §1.143

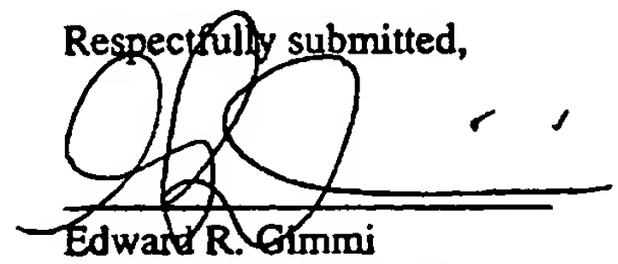
Sir:

This paper is in response to the Office Action dated 25 August 2003, setting forth a thirty (30) day shortened statutory period for reply. This response is being filed within said period, and no fees are believed due. However, authorization is hereby given to deduct any fees required by this paper to Deposit Account No. 19-2570, should any fees be due.

Claims 34-48 are subject to a restriction requirement. Upon review of the Detailed Action provided by the Examiner, Applicants provisionally elect Species Group A, wherein the T cell lymphocyte-mediated disease is rheumatoid arthritis, which is listed and/or referenced in Claims 34 and 39.

Applicants retain the right to file divisional applications on the non-elected subject matter, should the restriction requirement become final.

Respectfully submitted,



Edward R. Gimmi
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,836	07/13/2001	Peter John Bugelski	P50497C1	3846

7590 12/03/2003

GLAXOSMITHKLINE
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EXAMINER
GAMBEL, PHILLIP

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/905,836	BUGELSKI ET AL.	
	Examin r	Art Unit	
	Phillip Gambel	1644	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election of the species rheumatoid arthritis in treating immune cell-mediated diseases by administering CD4-specific antibodies in the Response, filed 9/22/03 is acknowledged.

Claims 34-48 are pending.

Claims 1-33 have been canceled previously.

2. Applicant should indicate on the first line of the specification to indicate the 120 and 119(e) priority documents.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

4. It does not appear that this application contains an Abstract of the disclosure as required by 37 CFR 1.72(b). An Abstract on a separate sheet is required.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 34-48 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of or immunosuppressive drugs or biopharmaceutical drugs can be species- and model-dependent, it is not clear that reliance on the in vivo experimental observations accurately reflects the relative ability of "administering a saturating dose of a CD4-specific monoclonal antibody".

Page 4, paragraph 3 of the instant specification defines "a saturating dose" as to the amount of therapeutic protein necessary to completely bind a selected immune cell antigen in the lymphatic system such that no appreciable binding of the therapeutic protein to the immune cell occurs upon subsequent administration of the therapeutic protein".

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

It has been well known to those skilled in the art that antibody therapy has been limited by a short half-life and human immune responses against therapeutic antibodies. In addition, the effect of antibody therapy depends on the nature of the surface antigen, the particular epitope and density of the antigen that binds the antibody and the isotype of the antibody itself. Further, cells can bind and thereby remove therapeutic antibodies from the circulation either by target antigen binding or Fc receptor binding.
CD4 is expressed by thymocytes, T cells, monocytes and bone marrow cells.
Therefore, it is not readily apparent that the skilled artisan would predict that a saturating dose to the degree defined by the specification as filed can be achieved throughout the lymphatic system in vivo.

For example, Lauerma et al. (Biodrugs 8: 96-106, 1997) discloses while CD4-specific antibodies have been tried in psoriasis; immunization against these CD4-specific antibodies have been a problem and nonimmunizing antibodies are not yet available for clinical use (see page 103, column 1; Monoclonal Antibodies).

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective antibody-based therapies based upon saturating doses; undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for achieving saturating doses of CD4-specific antibodies.

8. Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Claim 36: It is apparent that the CE9.1 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line / hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

9. Claims 34-48 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 34-48 are indefinite in the recitation set forth in independent claim 34;

i) because "a saturating dose" is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention;

ii) because it is not clear that the first administration of a saturation dose of the monoclonal antibody occurs subcutaneously; and

iii) because there is a lack of an antecedent basis for "the therapeutic protein form the second administration".

Applicant is invited to set forth clearly the method steps to carry out the claimed methods.

Alternatively, applicant is invited to explain clearly the methods steps, as currently recited.

B) Claim 36 is indefinite in the recitation of "CE9.1" because its characteristics are not known. The use of "CE9.1" monoclonal antibody as the sole means of identifying the claimed antibody and hybridoma renders the claim indefinite because "CE9.1" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct cell lines.

Applicant should indicate the appropriate Accession Number in addition to CD9.1.

C) Claim 47 should delete the recitation of "(i.e. 100%)" as this recitation is not appropriate claim language.

D) The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

10. No claim is allowed.

The claimed methods, drawn to a particular dosing regimen wherein the second subcutaneous administration of CD4-specific antibodies is at least 50% greater than the first subcutaneous systemic exposure, appears to be free of the prior art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

After January 20, 2004, Phillip Gambel's telephone number will be (571) 272-0844 and Christina Chan's telephone Number will be (571) 272-0841.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
December 1, 2003

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/905,836	07/13/2001	Peter John Bugelski	P50497C1	3846

7590 06/17/2004

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
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EXAMINER
GAMBEL, PHILLIP

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Notice of Abandonment	Application No. 09/905,836	Applicant(s) BUGELSKI ET AL.
	Examiner Phillip Gambel	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *03 December 2003*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 (a) to the final rejection.
   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).
   (c) ☐ A reply was received on _____, but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☒ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

Phillip Gambel
Primary Examiner 6/14/04
Art Unit: 1644
TECH CENTER 1600

Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.